#4

LAW OFFICES

KILYK & BOWERSOX, P.L.L.C.

Intellectual Property Law

LUKE A. KILYK* (PA, DC)
LEONARD D. BOWERSOX
JASBIR SINGH
MATTHEW T. GILL
RALPH T. WEBB* (DC, TX, LA)
SUSANNE M. HOPKINS

Of Counsel:
LAWRENCE B. BUGAISKY, Ph.D.* (DC)
WILLIAM CHARLES JAMISON, Ph.D.

*Admitted only in states indicated

53 A East Lee Street
WARRENTON, VA 20186

TEL.: (540) 428-1701
FAC.: (540) 428-1720
(540) 428-1721

FAIRFAX OFFICE
3603-E Chain Bridge Road
Fairfax, Virginia 22030

Email: lkilyk@kbpatentlaw.com
Website: http://www.kbpatentlaw.com

PLEASE DIRECT CORRESPONDENCE TO OUR WARRENTON OFFICE

FACSIMILE TRANSMISSION COVER SHEET

RECEIVED
30 JUN 2005
Legal Staff
International Division

DATE: June 30, 2005

TO: Mail Stop Petition
Attention: Brian Tung
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RE: International Application No. PCT/US02/39316
Entitled: NOVEL BENZODIFURANIMIDAZOLINE AND BENZOFURANIMIDAZOLINE DERIVATIVES AND THEIR USE FOR THE TREATMENT OF GLAUCOMA
Attorney Docket No. : 3010-036

FROM: Luke A. Kilyk, Esq.

FAC. TEL. NO.: 1-571-273-0459

NUMBER OF PAGES (INCLUDING THIS COVER SHEET): 71

Items Attached: Copy of U.S.P.T.O. date-stamped postcard – 1 page
Copy of U.S. Post Office Express Mail label – 1 page
Copy of Credit Card Payment Form – 1 page
Copy of Fee Transmittal – 1 page
Copy of Petition to Revive under 37 C.F.R. §1.137(b) with Attachments A & B – 66 pages

I hereby certify that this correspondence is being facsimile transmitted to the United States Patent and Trademark Office, Fax No. 1-571-273-0459 on June 30, 2005.

Kim Blum
Name (Print)

Kim Blum
Signature

07/08/2005 CSHOOT 00000002 500925 10525410
Sale Ref: 00000002 DAN: 500925 10525410
01 FC:1617 130.00 DA

07/01/2005 CSHOOT 00000001 PCT/US02/39316
01 FC:1631 300.00 OP
02 FC:2642 200.00 OP
03 FC:1632 500.00 OP
04 FC:1453 1500.00 OP

International Application No. PCT/US02/39316
Atty. Docket No. 2345F US (3010-036)
Filed: 9 December 2002 Applicant: Feng et al.
Entitled: NOVEL BENZODIFURANIMIDAZOLINE AND BENZOFURANIMIDAZOLINE DERIVATIVES AND THEIR USE FOR THE TREATMENT OF GLAUCOMA

Papers filed herewith on: April 5, 2005
Petition to Revive Under 37 C.F.R. § 1.137(b) with Attachments A and B, Transmittal Letter Concerning a Filing Under 35 U.S.C. 371, Application, Copy of Executed Declaration, Preliminary Amendment, Fee Transmittal, and Credit Card Payment Form (1,500.00)

Express Mail Label No. EV567360054US
COMMISSIONER FOR PATENTS
Receipt is hereby acknowledged of the papers filed as indicated in connection with the above-identified case

LAK/dsp

EV 567260054 US

Customer Copy
Label 11-F, April 2004

EXPRESS MAIL
UNITED STATES POSTAL SERVICE ●

Post Office To Addressee

ORIGIN: (POSTAL SERVICE USE ONLY)

PO ZIP Code	Day of Delivery	Postage
20186	☐ Next ☐ 2nd ☐ 3rd Del. Day	$ 17.85
Date Accepted	**Scheduled Date of Delivery**	**Return Receipt Fee**
Mo. 4 Day 5 Year	Month Day	$
Time Accepted	**Scheduled Time of Delivery**	**COD Fee** / **Insurance Fee**
☐ AM ☑ PM	☑ Noon ☐ 3 PM	$ / $
Flat Rate ☐ or **Weight**	**Military**	**Total Postage & Fees**
lbs. 12 4 ozs.	☐ 2nd Day ☐ 3rd Day	$ 17.85
	Int'l Alpha Country Code	**Acceptance Emp. Initials**

DELIVERY (POSTAL USE ONLY)

Delivery Attempt	Time	Employee Signature
Mo. Day	☐ AM ☐ PM	
Delivery Attempt	**Time**	**Employee Signature**
Mo. Day	☐ AM ☐ PM	
Delivery Date	**Time**	**Employee Signature**
Mo. Day	☐ AM ☐ PM	

No Delivery: ☐ Weekend ☐ Holiday

Customer Signature

CUSTOMER USE ONLY
METHOD OF PAYMENT:
Express Mail Corporate Acct. No. X220099
Federal Agency Acct. No. or Postal Service Acct. No.

FROM: (PLEASE PRINT) PHONE (540) 428-1701

KILYK & BOWERSOX PLLC
53A E LEE ST
WARRENTON VA 20186-5323

3040-036 (Petition to Revive)

TO: (PLEASE PRINT) PHONE (703) 308-4357

Mail Stop PCT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

FOR PICKUP OR TRACKING: Visit www.usps.com or Call 1-800-222-1811

USPS

PTO/SB/17 (10-03)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

FEE TRANSMITTAL for FY 2005

Effective 10/01/2003. Patent fees are subject to annual revision.

☐ Applicant Claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 1,500.00

Complete if Known	
International Application Number	PCT/US02/39316
International Filing Date	9 December 2002
First Named Inventor	Feng et al.
Examiner Name	Unassigned
Art Unit	Unassigned
Attorney Docket No.	2345F US (3010-036)

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☒ Credit card ☐ Money Order ☐ Other ☐ None

☒ Deposit Account

Deposit Account Number: 50-0925

Deposit Account Name: Kilyk & Bowersox, P.L.L.C.

The Director is authorized to: *(check all that apply)*

☐ Charge fee(s) indicated below ☒ Credit any overpayments

☒ Charge any additional fee(s) or any underpayment of fee(s)

☐ Charge fee(s) indicated below, except for the filing fee to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1011	300	2011	150	Utility filing fee	
1012	200	2012	100	Design filing fee	
1013	200	2013	100	Plant filing fee	
1014	300	2014	150	Reissue filing fee	
1005	200	2005	100	Provisional filing fee	

SUBTOTAL (1) ($) 0.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims		Fee from below		Fee Paid
Total Claims	-20**=	X		=	
Independent Claims	- 3**=	X		=	
Multiple Dependent				=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	50	2202	25	Claims in excess of 20
1201	200	2201	100	Independent claims in excess of 3
1203	360	2203	180	Multiple dependent claim, if not paid
1204	200	2204	100	**Reissue independent claims over original patent
1205	50	2205	25	**Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0.00

** or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge – late filing fee or oath	
1052	50	2052	25	Surcharge – late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	120	2251	60	Extension for reply within first month	
1252	450	2252	225	Extension for reply within second month	
1253	1020	2253	510	Extension for reply within third month	
1254	1590	2254	795	Extension for reply within fourth month	
1255	2,160	2255	1,080	Extension for reply within fifth month	
1401	500	2401	250	Notice of Appeal	
1402	500	2402	250	Filing a brief in support of an appeal	
1403	1,000	2403	500	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	500	2452	250	Petition to revive – unavoidable	
1453	1,500	2453	750	Petition to revive – unintentional	1,500.00
1501	1,400	2501	700	Utility issue fee (or reissue)	
1502	800	2502	400	Design issue fee	
1503	1,100	2503	550	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee for provisional applications	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	790	2809	395	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	790	2810	395	For each additional invention to be examined (37 CFR 1.129(b))	
1801	790	2801	395	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify)

*Reduced by Basic Filing Fee Paid SUBTOTAL (3) ($) 1,500.00

SUBMITTED BY

Complete (if applicable)

Name (Print/Type)	Luke A. Kilyk	Registration No. (Attorney/Agent)	33,251	Telephone	1-540-428-1701
Signature				Date	April 5, 2005

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

This collection of information is required by 37 CFR 1.17 and 1.27. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450. *If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

Date: April 5, 2005 Label No. EV567260054US I hereby certify that, on the date indicated above, I deposited this paper with identified attachments and/or fee with the U.S. Postal Service and that it was addressed for delivery to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 by "Express Mail Post Office to Addressee" service.

Donald S. Prater Donald S. Prater

Name (Print) Signature

Date: April 5, 2005 Label No. EV567260054US I hereby certify that, on the date indicated above, I deposited this paper with identified attachments and/or fee with the U.S. Postal Service and that it was addressed for delivery to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 by "Express Mail Post Office to Addressee" service.

Donald S. Prater — Donald S. Prater
Name (Print) Signature

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	FENG et al.
International Application No.:	PCT/US02/39316
International Filing Date:	9 December 2002
Docket No.:	2345F US (3010-036)

For: NOVEL BENZODIFURANIMIDAZOLINE AND BENZOFURANIMIDAZOLINE DERIVATIVES AND THEIR USE FOR THE TREATMENT OF GLAUCOMA

PETITION TO REVIVE UNDER 37 C.F.R. § 1.137(b)

Mail Stop PCT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

April 5, 2005

Sir:

This is a Petition Under 37 C.F.R. § 1.137(b) to revive an abandoned application, namely, the National Stage of International Application No. PCT/US02/39316 as permitted by M.P.E.P. 1893.02. As set forth below, each provision of 37 C.F.R. § 1.137(b) is satisfied and therefore, the applicants respectfully request the granting of this petition.

(1) In particular, attached as Attachment A are the necessary documents to accept this application as a national stage entry of International Application No. PCT/US02/39316. In particular, filed herewith is a copy of Form PTO-1390 which is a transmittal letter to the United States Designated/Elected Office concerning the filing under 35 U.S.C. § 371 as well as a copy of the International Application. Furthermore, the necessary fees are also authorized in the

transmittal letter for purposes of a § 371 entry. In addition, a copy of a declaration by the inventors is also attached. Accordingly, the necessary documents to accept this application as a national stage entry are satisfied.

(2) Furthermore, the petition fee as set forth in § 1.17(m) is provided with this petition.

(3) The entire delay in filing the required documents from the due date for the reply until the filing of a grantable petition pursuant to this paragraph was unintentional. In particular, the undersigned wishes to advise the U.S. Patent and Trademark Office that the due date for the national stage entry of this international application was June 21, 2004. On June 14, 2004, the applicants submitted the necessary transmittal letter under 35 U.S.C. § 371, the filing fee, an inventors' declaration, and a copy of the international application by express mail. However, the U.S. Patent and Trademark Office was not able to locate any information regarding this application and had no record of receiving it. On January 26, 2005, after contacting the U.S. PCT help desk in November and December of 2004, the applicants concluded that the documents must be lost and thereby proceeded to submit a Petition under 37 C.F.R. § 1.10 in order to have the U.S. Patent and Trademark Office recognize the filing of the documents submitted on June 14, 2004. However, in a Decision on Petition dated March 7, 2005, the U.S. Patent and Trademark Office decided that the provisions of 37 C.F.R. § 1.10(e) had not been fully satisfied in that the documents submitted on June 14, 2004, because the filed documents did not have the express mail label number on the documents. Therefore, the petition was denied. Upon this decision, the applicants immediately proceeded with contacting the undersigned and proceeded with this petition to revive the abandoned application as requested above. Copies of the original filing, including the Express Mail label with the U.S. Postal Service date stamp, as well as the

Petition under 37 C.F.R. § 1.10, as well as the Decision on Petition under 37 C.F.R. § 1.10(e) are set forth as Attachment B.

It is respectfully submitted that in view of this information, the abandonment of this application was unintentional and that the filing of this Petition to Revive is timely and that the "delay in filing the required reply from the due date for the reply until the filing of a grantable petition pursuant to this paragraph" was clearly unintentional.

4). Applicants believe that no Terminal Disclaimer is required pursuant to paragraph (b) of 37 C.F.R. § 1.137.

The undersigned and the applicants note that under the provisions under M.P.E.P. § 1893.02, the U.S. Patent and Trademark Office does recognize the revival of an International Application designating the United States if the requirements of 35 U.S.C. § 371(c) are not complied with by the time period set forth in 37 C.F.R. § 1.495(b) and (c). The application will be considered abandoned but that the applicants may file a Petition to Revive an abandoned application in accordance with the provisions of 37 C.F.R. §1.137. The applicants submit that this is the present situation and therefore this petition would be a suitable petition for the current fact pattern.

By the filing of this Petition to Revive, the applicants do not admit that the originally filed National Stage Entry on June 14, 2004 was untimely, incomplete, improper, or deficient. However, in order to expedite and proceed with the prosecution of this application, the Petition to Revive was seen as the best means to resolve this matter in view of the disagreement that currently exists between the U.S. Patent and Trademark Office and the applicants.

Accordingly, in view of the information set forth above, as well as the documentation provided herein, the U.S. Patent and Trademark Office is respectfully requested to grant this

International Application N[redacted]PCT/US02/39316
Petition to Revive Under 37 C.F.R. § 1.137(b)

Petition to Revive the abandoned application.

CONCLUSION

If there are any fees due in connection with the filing of this Request for Reconsideration, please charge the fees to Deposit Account No. 50-0925. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such extension is requested and should also be charged to our Deposit Account.

Respectfully submitted,

Luke A. Kilyk
Registration No. 33,251

Attorney Docket No. 2345F US (3010-036)
KILYK & BOWERSOX, P.L.L.C.
53 A East Lee Street
Warrenton, VA 20186
Tel.: (540) 428-1701
Fax: (540) 428-1720

ATTACHMENT A

PTO-1390 (Rev. 12-2004)
Approved for use through 03/31/2007. OMB 0651-0021
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. Application No. (If known, see 37 CFR 1.5)	
2345F US (3010-038)	Unknown	
INTERNATIONAL APPLICATION NO. PCT/US02/39316	INTERNATIONAL FILING DATE 9 December 2002	PRIORITY DATE CLAIMED 20 December 2001

TITLE OF INVENTION: NOVEL BENZODIFURANIMIDAZOLINE AND BENZOFURANIMIDAZOLINE DERIVATIVES AND THEIR USE FOR THE TREATMENT OF GLAUCOMA

APPLICANT(S) FOR DO/EO/US: Zixia FENG and Mark R. HELLBERG

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This is an express request to begin national examination procedures (35 U.S.C. 371 (f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. [X] The US has been elected (Article 31).
5. [X] A copy of the International Application as filed (35 U.S.C. 371 (c)(2))
   a. [X] is attached hereto (required only if not communicated by the International Bureau).
   b. [ ] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] An English language translation of the International Application as filed (35 U.S.C. 371 (c)(2)).
   a. [X] is attached hereto.
   b. [ ] has been previously submitted under 35 U.S.C. 154(d)(4).
7. [X] Amendments to the claims of the International Application under PCT Article 34 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3))
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A preliminary amendment.
14. [ ] An Application Data Sheet under 37 CFR 1.76
15. [ ] A substitute specification.
16. [ ] A power of attorney and/or address change letter.
17. [ ] A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 – 1.825.
18. [ ] A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. [ ] A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. [X] Other items or information:
    Petition to Revive Under 37 C.F.R. § 1.137(b) and Fee Transmittal

PTO-1390 (Rev. 12-2004)
Approved for use through 03/31/2007. OMB 0651-0021
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
Unknown	PCT/US02/39316	2345F US (3010-036)

21. [x] The following fees are submitted:			
[x] a) Basic national fee $300.00		$ 300.00	
[x] b) Examination fee $200.00		$ 200.00	
[x] c) Search fee $500.00		$ 500.00	
TOTAL OF ABOVE CALCULATIONS = $ 1,000.00		$ 1,000.00	
[ ] Additional fee for specification and drawings filed in paper over 100 sheets (excluding sequence listing or computer program listing filed in an electronic medium). The fee is **$250.00** for each additional 50 sheets of paper or fraction thereof.			
Total Sheets: 31 - 100 =	Extra sheets: /50 =	Number of each additional 50 or fraction thereof (round up to a whole number): 0	x $250.00
			$ 0.00
Surcharge of **$130.00** for furnishing the oath or declaration later than Months from the earliest claimed priority date (37 CFR 1.492(e)).			$ 0.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	16 - 20 =	0	x **$50.00**	$ 0.00
Independent claims	3 - 3 =	0	x **$200.00**	$ 0.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$360.00**	$ 0.00
TOTAL OF ABOVE CALCULATIONS =				$ 1,000.00
[ ] Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by ½.				$ 0.00
SUBTOTAL =				$ 1,000.00
Processing fee of **$130.00** for furnishing the English translation later than months from the earliest claimed priority date (37 CFR 1.492(f)).				$ 0.00
TOTAL NATIONAL FEE =				$ 1,000.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$ 0.00
TOTAL FEES ENCLOSED =				$ 1,000.00
			Amount to be: Refunded	$
			Amount to be Charged	$

a. [ ] A check in the amount of $ _____ to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. _____ in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [x] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 50-0925.

d. [x] Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO

KILYK & BOWERSOX, P.L.L.C.
53 A East Lee Street
Warrenton, VA 20186

Phone (540) 428-1701 - Facsimile (540) 428-1720

SIGNATURE:

Luke A. Kilyk
NAME

33,251
REGISTRATION NUMBER

Form PTO-1390 (REV 12-2001)

Date: April 5, 2005 Label No. EV567260054US I hereby certify that, on the date indicated above, I deposited this paper with identified attachments and/or fee with the U.S. Postal Service and that it was addressed for delivery to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 by "Express Mail Post Office to Addressee" service.

Donald S. Prater
Name (Print)

Signature

Rec'd 26 JAN 2005

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

10/525410

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 July 2003 (03.07.2003)

PCT

(10) International Publication Number
WO 03/053436 A1

(51) International Patent Classification[7]: A61K 31/4178, C07D 403/06

(21) International Application Number: PCT/US02/39316

(22) International Filing Date: 9 December 2002 (09.12.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/343,378 20 December 2001 (20.12.2001) US

(71) Applicant (for all designated States except US): ALCON, INC. [CH/CH]; P. O. Box 62, Bösch 69, CH-6331 Hünenberg (CH).

(72) Inventors; and
(75) Inventors/Applicants (for US only): FENG, Zixia [US/US]; 4204 Hideaway Drive, Arlington, TX 76017 (US). HELLBERG, Mark, R. [US/US]; 2545 Glen Ridge Drive, Highland Village, TX 75077 (US).

(74) Agents: SCHULTZ, Teresa, J. et al.; ALCON RESEARCH, LTD., R & D Counsel, Q-148, 6201 South Freeway, Fort Worth, TX 76134-2099 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR).

Declaration under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR)*

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/053436 A1

(54) Title: NOVEL BENZODIFURANIMIDAZOLINE AND BENZOFURANIMIDAZOLINE DERIVATIVES AND THEIR USE FOR THE TREATMENT OF GLAUCOMA

(57) Abstract: The present invention provides benzodifuran imidazoline derivatives and benzofuran imidazoline derivatives for lowering intraocular pressure and providing ocular neuroprotection.

NOVEL BENZODIFURANIMIDAZOLINE AND BENZOFURANIMIDAZOLINE DERIVATIVES AND THEIR USE FOR THE TREATMENT OF GLAUCOMA

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to the field of glaucoma treatment and ocular neuroprotection. More particularly, the present invention provides novel compounds, compositions and methods for treating glaucoma, lowering intraocular pressure and providing neuroprotection.

2. Description of the Related Art

The disease state referred to as glaucoma is characterized by a permanent loss of visual function due to irreversible damage to the optic nerve. The several morphologically or functionally distinct types of glaucoma are typically characterized by elevated IOP, which is considered to be causally related to the pathological course of the disease. Ocular hypertension is a condition wherein intraocular pressure is elevated but no apparent loss of visual function has occurred; such patients are considered to be at high risk for the eventual development of the visual loss associated with glaucoma. Some patients with glaucomatous field loss have relatively low intraocular pressures. These so called normal tension or low tension glaucoma patients can also benefit from agents that lower and control IOP. If glaucoma or ocular hypertension is detected early and treated promptly with medications that effectively reduce elevated intraocular pressure, loss of visual function or its progressive deterioration can generally be ameliorated. Drug therapies that have proven to be effective for the reduction of intraocular pressure include both agents that decrease aqueous humor production and agents that increase the outflow facility.

Such therapies are in general administered by one of two possible routes, topically (direct application to the eye) or orally.

There are some individuals who do not respond well when treated with certain existing glaucoma therapies. There is, therefore, a need for other topical therapeutic agents that control IOP.

Serotonin (5-hydroxy tryptamine; 5HT) is an endogenous biogenic amine with a well defined neurotransmitter function in many tissues of the body including the eye [Zifa and Fillion 1992; Hoyer *et al.* 1994; Tobin *et al.* 1988].

5HT is known to interact with at least seven major 5HT receptors ($5HT_1$ - $5HT_7$), and additional subtypes within these families, to initiate intracellular biochemical events such as stimulation of second messengers (e.g. cAMP, inositol trisphosphate) eventually leading to the final biological response, for example, tissue contraction or hormone release, etc. [Hoyer *et al.* 1994; Martin *et al.* 1998]. Receptor subtypes within the $5HT_1$ family are negatively coupled to adenylyl cyclase (AC) and cause inhibition of cAMP production, while $5HT_4$, $5HT_6$, and $5HT_7$ receptors are positively coupled to AC and thus stimulate cAMP production when activated by 5HT [Martin *et al.* 1998]. The receptors in the $5HT_2$ family are positively coupled to phospholipase C (PLC) and thus generate inositol phosphates and mobilize intracellular calcium when activated to mediate the effects of 5HT. The $5HT_3$ receptor is unique in that it couples to an ion channel which gates sodium, potassium, and calcium [Hoyer *et al.* 1994].

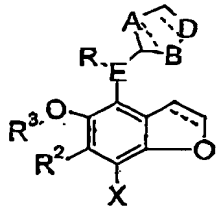
Known compounds exhibiting $5HT_2$ agonist activity have typically been designed to treat numerous central nervous system (CNS)-related conditions, particularly the treatment of obesity and depression, by activation of $5\text{-}HT_{2C}$ receptors. Thus, one desired property of known $5HT_2$ agonist compounds is that they easily penetrate the blood brain barrier. Compounds that readily penetrate the blood-brain-barrier by passive diffusion are generally lipophilic molecules, which do not contain polar functional groups that might impede this diffusion.

The utility of $5\text{-}HT_2$ agonists for controlling IOP in the monkey model of glaucoma has been established (WO 00/16761). α_2 adrenoceptor agonists are also known for their use as IOP lowering agents. It is also known that compounds with $5\text{-}HT_{1A}$ agonist activity can be useful for the treatment of glaucomatous optic neuropathy (WO 0170223 A1). Until the present invention, no single compound possessing $5\text{-}HT_{2A}$ and/or $5\text{-}HT_{1A}$ agonist activity along with α_2 adrenoceptor agonist activity has been known.

To treat ocular diseases, it is desirable to administer topically compositions that will remain in the ocular tissues and not cross the blood brain barrier and enter the CNS. What are needed are anti-glaucoma drugs with both IOP lowering potency and ocular neuroprotective activity. It is also desirable that such compounds would not have a propensity to cross the blood brain barrier.

SUMMARY OF THE INVENTION

The present invention overcomes these and other drawbacks of the prior art by providing benzodifuran imidazoline derivatives and benzofuran imidazoline compounds for lowering IOP and providing neuroprotection. More specifically, the present invention provides compounds of the formula:



wherein A, B and D are independently chosen from either N or C, with the provision that at least one of A, B or D is N; E is C or N; R is H or C_{1-4}alkyl; R^2 and R^3 are independently H, C_{1-3} alkyl, C_{2-3} alkenyl, or R^2 and R^3 taken together can form a 5 or 6 member ring; X is hydrogen, halogen, C_{1-4}alkyl, or CF_3; and the dashed bond may be a single bond or a double bond; and pharmaceutically acceptable salts and solvates. Preferably the compound is 2-(8-bromo-benzo-[1,2-b;4,5-b']difuran-4-yl) imidazoline hydrochloride.

In another aspect, the present invention provides compositions containing the compounds described above. The compositions are most preferably in the form of topical ophthalmic formulations for delivery to the eye. The compounds of the invention may be combined with ophthalmologically acceptable preservatives, surfactants, viscosity enhancers, penetration enhancers, buffers, sodium chloride, and water to form an aqueous, sterile ophthalmic suspension or solution to form the compositions of the invention.

The compositions of the invention are preferably formulated as topical ophthalmic suspensions or solutions, with a pH of about 5 to 8. The compounds of the invention as described above will normally be contained in these formulations in an amount .01% to 5% by weight, but preferably in an amount of 0.1% to 2% by weight. Thus, for topical presentation 1 to 2 drops of these formulations would be delivered to the surface of the eye 1 to 4 times per day according to the routine discretion of a skilled clinician.

The present invention further provides a method of lowering intraocular pressure and providing ocular neuroprotection in a mammal by administering to a patient in need thereof a therapeutically effective amount of a composition comprising a compound having the structure as described above. In preferred embodiments, the composition can be administered locally to the eye (e.g., topically, intracamerally, or via an implant).

DETAILED DESCRIPTION PREFERRED EMBODIMENTS

Unexpectedly, it has been found that serotonergic compounds which possess agonist activity at $5HT_2$ receptors effectively lower and control elevated IOP and glaucoma. In addition, the compounds provide neuroprotective activity and are useful for treating persons suffering from ocular diseases associated with neuronal cell death.

It has been found that serotonergic compounds which possess agonist activity at 5-HT_2 receptors effectively lower and control normal and elevated IOP and are useful for treating glaucoma, see commonly owned co-pending application, PCT/US99/19888.

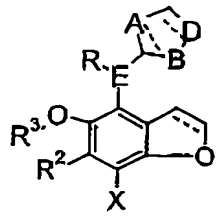
Compounds that act as agonists at 5-HT_2 receptors are known and have shown a variety of utilities, primarily for disorders or conditions associated with the central nervous

system (CNS). U.S. Patent 5,494,928 discloses certain 2-(indol-1-yl)-ethylamine derivatives that are 5-HT_{2C} agonists for the treatment of obsessive compulsive disorder and other CNS derived personality disorders. U.S. Patent 5,571,833 discloses tryptamine derivatives that are 5-HT_2 agonists for the treatment of portal hypertension and migraine. U.S. Patent 5,874,477 discloses a method for treating malaria using 5-$HT_{2A/2C}$ agonists. U.S. Patent 5,902,815 discloses the use of 5-HT_{2A} agonists to prevent adverse effects of NMDA receptor hypo-function. WO 98/31354A2 discloses 5-HT_{2B} agonists for the treatment of depression and other CNS conditions. Agonist response at the 5-HT_{2A} receptor is reported to be the primary activity responsible for hallucinogenic activity, with some lesser involvement of the 5-HT_{2C} receptor possible (Fiorella *et al.* 1995).

Serotonergic 5-HT_{1A} agonists have been reported as being neuroprotective in animal models and many of these agents have been evaluated for the treatment of acute stroke among other indications. This class of compounds has been disclosed for the treatment of glaucoma (lowering and controlling IOP), see *e.g.*, WO 98/18458 and EP 0771563A2. Osborne *et al.* teach that 8-hydroxydipropylaminotetralin (8-OH-DPAT) (a 5-HT_{1A} agonist) reduces IOP in rabbits (Osborne *et al.* 1996). Wang *et al.* disclose that 5-methylurapidil, an α_{1A} antagonist and 5-HT_{1A} agonist lowers IOP in the monkey, but due to its α_{1A} receptor activity (Wang *et al.* 1997; Wang *et al.* 1998). Also, 5-HT_{1A} antagonists are disclosed as being useful for the treatment of glaucoma (elevated IOP) (*e.g.* WO 92/0338). Furthermore, DeSai *et al.* (WO 97/35579) and Macor *et al.* (U.S. 5,578,612) disclose the use of 5-HT_1 and 5-$HT_{1\text{-like}}$ agonists for the treatment of glaucoma (elevated IOP). These anti-migraine compounds are 5-$HT_{1B,D,E,F}$ agonists, e.g., sumatriptan and naratriptan and related compounds.

The present invention provides compounds possessing α_2 adrenoceptor agonist activity along with 5-HT_{2A} and 5-HT_{1A} activities having the general structure of Formula I.

Formula I



wherein A, B and D are independently chosen from ether N, C, with the provision that at least one of A, B or D is N; E is C or N; R is H, C_{1-4}alkyl; R^2 is H, C_{1-3} alkyl, or C_{2-3} alkenyl; R^3 is H, C_{1-3} alkyl, or C_{2-3} alkenyl; or R^2 and R^3 taken together can form a 5 or 6 member ring; X is chosen from hydrogen, halogen, C_{1-4}alkyl, CF_3; the dashed bond indicates that either a single bond or a double bond can exist at this bond location; and pharmaceutically acceptable salts and solvates. In preferred embodiments, the compound of the invention is 2-(8-bromo-benzo-[1.2-b;4,5-b']difuran-4-yl) imidazoline hydrochloride.

ES 323985 discusses that oxymetazoline is currently used for nasal de-congestion and in an ophthalmic solution to relieve redness of the eye. Although ES 323985 does discuss IOP lowering activity for oxymetazoline, it does not discuss the use of oxymetazoline for lowering IOP and ocular neuroprotection. Moreover, oxymetazoline is not a benzofuran as it lacks the furan substituent(s) and/or the ether substituent (Wang *et al.* 1993). Further, none of the claimed compounds are disclosed in ES 323985 or Wang.

It is recognized that compounds of Formula I can contain one or more chiral centers. This invention contemplates all enantiomers, diastereomers and, mixtures thereof.

In the above definitions, the total number of carbon atoms in a substituent group is indicated by the $C_{i,j}$ prefix where the numbers i and j define the number of carbon atoms; this definition includes straight chain, branched chain, and cyclic alkyl or (cyclic alkyl)alkyl groups.

It is important to recognize that a substituent may be present either singly or multiply when incorporated into the indicated structural unit. For example, the substituent halogen, which means fluorine, chlorine, bromine, or iodine, would indicate that the unit to which it is attached may be substituted with one or more halogen atoms, which may be the same or different.

The compounds of the invention can be administered systemically or locally to the eye (e.g., topically, intracamerally, or via an implant). The compounds are preferrably incorporated into topical ophthalmic formulations for delivery to the eye. The compounds may be combined with ophthalmologically acceptable preservatives, surfactants, viscosity enhancers, penetration enhancers, buffers, sodium chloride, and water to form an aqueous, sterile ophthalmic suspension or solution. Ophthalmic solution formulations may be prepared by dissolving a compound in a physiologically acceptable isotonic aqueous buffer. Further, the ophthalmic solution may include an ophthalmologically acceptable surfactant to assist in dissolving the compound. Additionally, the ophthalmic solution may contain an agent to increase viscosity, such as, hydroxymethylcellulose,

hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, or the like, to improve the retention of the formulation in the conjunctival sac. Gelling agents can also be used, including, but not limited to, gellan and xanthan gum. In order to prepare sterile ophthalmic ointment formulations, the active ingredient is combined with a preservative in an appropriate vehicle, such as, mineral oil, liquid lanolin, or white petrolatum. Sterile ophthalmic gel formulations may be prepared by suspending the active ingredient in a hydrophilic base prepared from the combination of, for example, carbopol-940, or the like, according to the published formulations for analogous ophthalmic preparations; preservatives and tonicity agents can be incorporated.

The compounds of the invention are preferably formulated as topical ophthalmic suspensions or solutions, with a pH of about 5 to 8. The compounds will normally be contained in these formulations in an amount .01% to 5% by weight, but preferably in an amount of 0.1% to 2% by weight. Thus, for topical presentation 1 to 2 drops of these formulations would be delivered to the surface of the eye 1 to 4 times per day according to the routine discretion of a skilled clinician.

The compounds can also be used in combination with other IOP lowering agents, such as, but not limited to, β-blockers, prostaglandins, carbonic anhydrase inhibitors, and miotics. The compounds can also be used in combination with other agents useful for treating glaucoma, such as, but not limited to, calcium channel blockers and NMDA antagonists. These agents may be administered topically, but usually systemically.

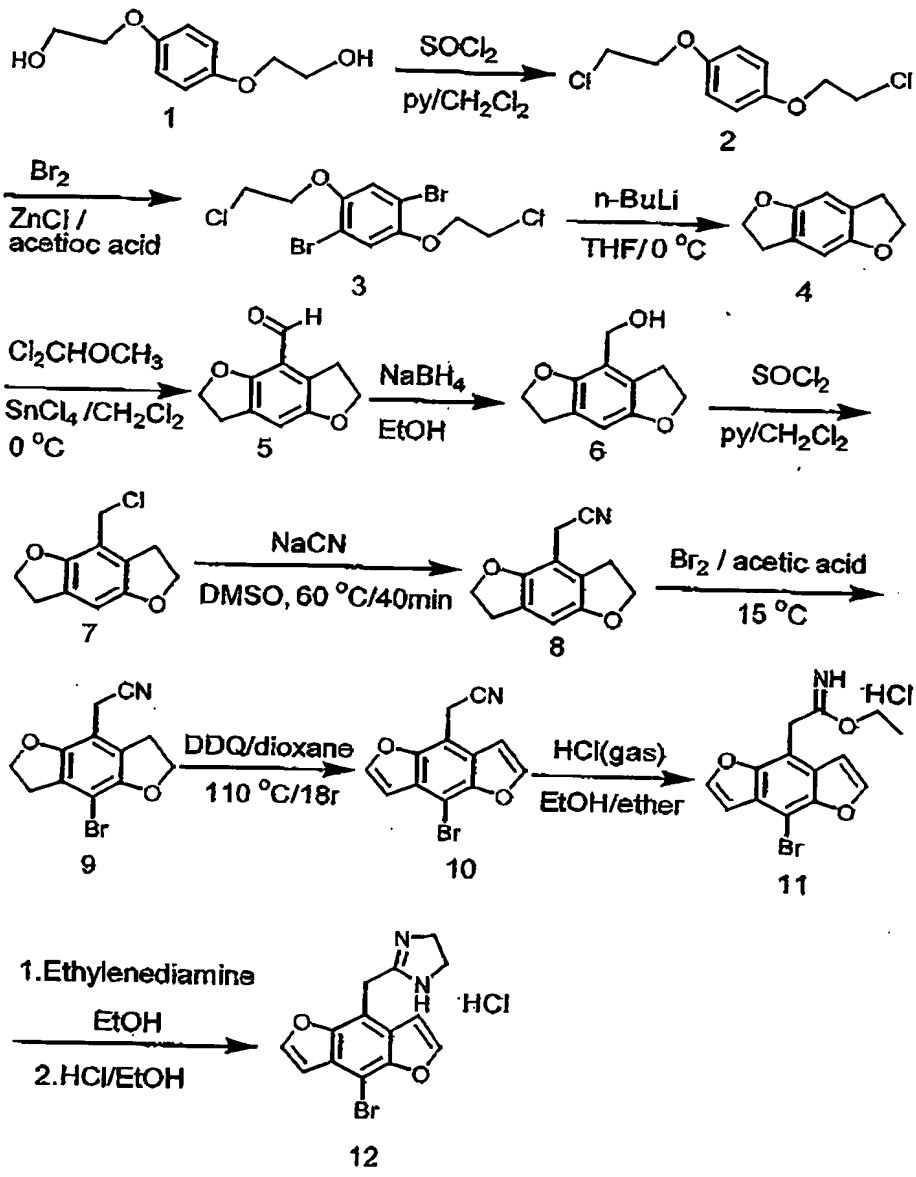
The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

Example 1 Synthetic Scheme for 2-(8-bromo-benzo-[1,2-b;4,5-b']difuran-4-yl) imidazoline hydrochloride

Examples of the compounds of this invention may be prepared by the synthetic route describe by Scheme 1. Briefly , the commercially available bis ethanol ether is treated with thionyl chloride in the presence of a organic base preferably pyridine in a solvent such as methylene chloride to form 2. The halogenated ether 2 is brominated using bromine in the presence of a Lewis acid such as zinc chloride in a solvent such as acetic acid to give compound 3. The di-bromide is cyclized to 4 with n-butyl lithium in a solvent such as dioxane or tetrahydrofuran maintained at a temperature of –40 to 0° C. Formylation with dichloromethyl methyl ether in the presence of stannic chloride in an inert solvent such as methylene chloride provides 5. Reduction of the aldehyde with sodium borohyride in a solvent such as ethanol or isopropyl alcohol yields the alcohol 6. The alcohol is converted to the chloride 7 by treatment with thionyl chloride in the presence of pyridine in a solvent such as methylene chloride. The nitrile 8 is formed by reacting 7 with sodium cyanide in a solvent such as DMSO at a temperature of 40-80° C. Bromination of the nitrile with a mixture of bromine and acetic acid at temperatures 0 to

20° C yields compound 9. Reduction of the bis dihydrofuran with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in a solvent such as dioxane at temperatures between 80 to 130° C yields compound 10. Treatment of the nitrile 10 with hydrogen chloride gas in a solution of ethanol and ether provides the imino ester, 11. Cyclization of the imino ester with ethylenediamine in ethanol and conversion of the product to the hydrochloride salt using a solution of hydrogen chloride in ethanol yields imidazoline benzodifuran 12.

Scheme 1


HO
OH
1
SOCl2
py/CH2Cl2
Cl
Cl
2
Br2
ZnCl /
acetioc acid
Br
Br
3
n-BuLi
THF/0 °C
4
Cl2CHOCH3
SnCl4 /CH2Cl2
0 °C
5
NaBH4
EtOH
6
SOCl2
py/CH2Cl2
7
NaCN
DMSO, 60 °C/40min
8
Br2 / acetic acid
15 °C
9
DDQ/dioxane
110 °C/18r
10
HCl(gas)
EtOH/ether
11
1.Ethylenediamine
EtOH
2.HCl/EtOH
12

Example 2 2-(8-bromo-benzo-[1,2-b;4,5-b']difuran-4-yl) imidazoline hydrochloride

2-(8-Bromo-benzo-[1,2-b;4,5-b']difuran-4-yl) imidazoline hydrochloride was prepared by the multi-step procedure described below.

Step A: 1,4-Bis(2-chloroethoxy)benzene

Bis(2-hydroxyethyl)hydroquinone (50g, 0.25mol) was dissolved in 500ml of CH_2Cl_2 and cooled to 0° C, pyridine (48ml, 0.6mol) and thionyl chloride (41ml, 0.58ml) were added dropwise such that the temperature did not exceed 5 °C. The mixture was allowed to warm to room temperature and was stirred over night. The solvent volume was reduced to 150ml. Aqueous 2N HCl (150ml) was added slowly and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3x100ml). The combined organic layer was washed with 2N HCl (150ml), saturated NaCl solution (150ml), dried over anhydrous $MgSO_4$, filtered and evaporated to a white solid. Recrystallization from ethanol afforded a white solid (73g). CIMS *m/z* 236 $(M+H)^+$.

Step B: 1,4-Bis(2-chloroethoxy)-2,5-dibromobenzene

1,4-Bis(2-chloroethoxy)benzene (40g, 0.17mol) was suspended in acetic acid (400ml) and zinc chloride (56g, 0.41mol) was added. Bromine (57, 0.36mol) dissolved in acetic acid (80ml) was added dropwise to the suspension over 1.5h. The reaction was stirred at room temperature over night, during which time a precipitate formed. The solids were filtered, washed with acetic acid and ethanol and dried. A crystalline white product was obtained (45g). CIMS *m/z* 393 $(M+H)^+$.

Step C: 2,3,6,7-Tetrahydrobenzol[1,2-b;4,5-b']difuran

A solution of 1,4-Bis(2-chloroethoxy)-2,5-dibromobenzene (15g, 0.036mol) in dry THF (300ml) was cooled to 0 °C under nitrogen. A solution of 2.5 M n-butyl lithium in hexane (30ml, 0.075mol) was added through a syringe very quickly to the well stirred solution. The reaction mixture was stirred at 0 °C for 10 min, and the solvent was removed *in vacuo*. The residue was partitioned between ether (300ml) and water (200ml). The organic layer was washed with water (200 ml), dried over $MgSO_4$ and filtered. The solution was evaporated on a rotary evaporator until solids formed. The solids were filtered and dried to afford 4.3g of 2,3,6,7-tetrahydrobenzol[1,2-b;4,5-b']difuran. CIMS *m/z* 163 $(M+H)^+$.

Step D: 4-Formyl-2,3,6,7-tetrahydrobenzol[1,2-b;4,5-b']difuran

Tin(IV) chloride (11.7 ml, 0.1mol) was added through a syringe to a solution of 2,3,6,7-tetrahydrobenzol[1,2-b;4,5-b']difuran (12.6 g, 0.078 mol) in 300 ml of dry CH_2Cl_2 at 0 °C under N_2, and the mixture was stirred for 5 min. Dichloromethyl methyl ether (7 ml, 0.078 mol) in 20 ml of CH_2Cl_2 was added into the mixture dropwise over a 10 min period. After the mixture was stirred for 30 min, the reaction was quenched by the addition of 100 ml of ice water. The aqueous layer was extracted with CH_2Cl_2 (2x100ml). The organic layers were combined and the resulting solution was washed with 3N HCl (3x150ml), H_2O (200 ml), and a saturated NaCl solution (200ml), dried over anhydrous $MgSO_4$, filtered and evaporated to a white solid. Recrystallization from CH_2Cl_2-hexane yielded 12.2 g of the product as a yellow solid. CIMS *m/z* 191 $(M+H)^+$.

Step E: 4-Hydroxymethyl-2,3,6,7-tetrahydrobenzol[1,2-b;4,5-b']difuran

A solution of $NaBH_4$ (2g, 0.053 mol) in 40 ml of 90% EtOH was added dropwise to a solution of 4-Formyl-2,3,6,7-tetrahydrobenzol[1,2-b;4,5-b']difuran (10 g, 0.053 mol) in 200 ml of EtOH. The solution was stirred at room temperature for 30 min and at 60° C for 10 min. After cooling to 0° C, 5 ml of 1N HCl was added and the solvent was evaporated. Ethyl acetate (80 ml) was added to the residue, and the resulting mixture was washed with H_2O (50 ml), saturated NaCl solution (50ml), dried over anhydrous $MgSO_4$, filtered and evaporated to a residue. Chromatography of the residue on silica gel, eluting with 30 % ethyl acetate in hexane, gave 7.5 g of 4-hydroxymethyl-2,3,6,7-tetrahydrobenzol[1,2-b;4,5-b']difuran as a white solid. CIMS *m/z* 193 $(M+H)^+$.

Step F: 4-Chloromethyl-2,3,6,7-tetrahrdrobenzol[1,2-b;4,5-b']difuran

Pyridine (4 ml, 0.05 mol) was added to a solution of 4-hydroxymethyl-2,3,6,7-tetrahrdrobenzol[1,2-b;4,5-b']difuran (4 g, 0.021 mol) in 50 ml of CH_2Cl_2 and the mixture was cooled to 0 °C. Thionyl chloride (3.5 ml, 0.048 mol) was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred for 6 h. After cooling, the mixture was washed with 1 N NaOH (2x50 ml), saturated NaCl solution (100ml), dried over anhydrous $MgSO_4$, filtered and evaporated to a residue. Chromatography of the residue on silica gel, eluting with 10 % ethyl acetate in hexane, gave 2.5 g of the product as a white solid. CIMS *m/z* 211 $(M+H)^+$.

Step G: 4-Acetonitrile-2,3,6,7-tetrahrdrobenzol[1,2-b;4,5-b']difuran

4-Chloromethyl-2,3,6,7-tetrahydrobenzol[1,2-b;4,5-b']difuran (2 g, 0.01 mol) in 20 ml of DMSO was added dropwise to a solution of sodium cyanide (0.75 g, 0.015 mol) in 20 ml of DMSO at 70 °C. The mixture was stirred at 70 °C for 40 min. After cooling, 50 ml of ice-water was added. The precipitate formed was filtered, washed with water and dried giving white solid 8 (1.4g). CIMS *m/z* 202 $(M+H)^+$.

Step H: 4-Acetonitrile-8-bromo-2,3,6,7-tetrahrdrobenzol[1,2-b;4,5-b'] difuran

Bromine (1.1 g, 0.007 mol) in 10 ml of acetic acid was added dropwise to a suspension of 4-acetonitrile-2,3,6,7-tetrahydrobenzol[1,2-b;4,5-b']difuran (1.4 g, 0.007 mol) in 20 ml of acetic acid at 15° C. The mixture was stirred at 15° C for 15 min. The precipitate formed was filtered, washed with acetic acid and ethanol and dried to yield 1.4 g of the product as a white solid. CIMS *m/z* 281 $(M+H)^+$.

Step I: 4-Acetonitrile-8-bromo-[1,2-b;4,5-b']difuran

A solution of DDQ in 70 ml of dioxane was added dropwise to a solution of 4-acetonitrile-8-bromo-2,3,6,7-tetrahrdrobenzol[1,2-b;4,5-b']difuran (1.4g, 0.005 mol) in 70 ml of dioxane. The mixture was stirred at reflux for 24 h. After cooling, the precipitate that formed was filtered and washed with dioxane. The filtrate was evaporated to a residue, which was subjected to chromatography on silica gel, eluting with 10 % ethyl acetate in hexane, to yield 0.61 g of 10 as a white solid. CIMS *m/z* 277 $(M+H)^+$, mp 169-170° C.

Step J: Ethyl (8-bromo-[1,2-b;4,5-b']difuran- 4-yl)acetimidate hydrochloride

An excess of dry HCl gas was passed through a solution of 4-acetonitrile-8-bromo-[1,2-b;4,5-b']difuran (0.6 g, 0.0022 mol) in 50 ml of anhydrous ether and 3 ml of absolute ethanol at 0 °C. The resulting mixture was allowed to stirred at 0 °C for 1 h and at room temperature over night. The white solid formed was collected by filtration, washed with ether and dried to give white crystal of the product (0.6 g). ESMS *m/z* 323 $(M+H)^+$, mp 239-240 °C (dec).

Step K: 2-(8-Bromo-benzo-[1,2-b;4,5-b']difuran- 4-yl)imidazoline hydrochloride

A solution of ethylenediamine (0.8 ml, 0.012 mol) in absolute ethanol (5 ml) was added dropwise to a suspension of ethyl (8-bromo-[1,2-b;4,5-b']difuran-4-yl)acetimidate hydrochloride (0.54 g, 0.0015 mol) in absolute ethanol (50 ml) at 0° C. The resulting mixture was stirred at 0° C for 1 h and then refluxed for 20 min. The solvent was evaporated and the residue was dissolved in 20 ml of ethanol. A solution of 1N HCl in ether was added to the solution above to reach a pH of 3 and the mixture was stirred at room temperature overnight. The white solid that formed (0.4 g) was filtered, dried and recrystallized from MeOH/ether to afford the product (0.32 g). APCIMS *m/z* 320 $(M+H)^+$, mp 264-265° C (dec). ^1H NMR ($CDCl_3$) □ 8.21-8.19 (s, 2H), 7.43 (s, 1H), 7.08 (s, 1H), 4.47 (s, 2H), 3.83 (s, 4H), 3.32 (s, 2H), ^{13}C NMR ($CDCl_3$) □ 168.10 (C), 149.45 (C), 148.49 (C), 147.99 (CH), 147.63 (CH), 126.26 (C), 126.13 (C), 106.64 (CH), 106.53 (CH), 106.24 (C), 93.40 (C), 44.24 (CH_2), 24.15 (CH_2). Anal.

($C_{14}H_{11}BrN_2O_2 \cdot HCl$), Cal: C, 47.29%; H, 3.40%; N, 7.87%; found: C, 47.05%; H, 3.56%; N, 7.98%.

Example 3 5-HT_2 Receptor Binding Assay

In order to determine the relative affinities of serotonergic compounds at the 5-HT_2 receptors, their ability to compete for the binding of the agonist radioligand [^{125}I]DOI to brain 5-HT_2 receptors is determined as described below with minor modification of the literature procedure (Johnson *et al.* 1987). Aliquots of post mortem rat cerebral cortex homogenates (400 µl) dispersed in 50 mM TrisHCl buffer (pH 7.4) are incubated with [^{125}I]DOI (80 pM final) in the absence or presence of methiothepin (10 µM final) to define total and non-specific binding, respectively, in a total volume of 0.5 ml. The assay mixture is incubated for 1 hour at 23°C in polypropylene tubes and the assays terminated by rapid vacuum filtration over Whatman GF/B glass fiber filters previously soaked in 0.3% polyethyleneimine using ice-cold buffer. Test compounds (at different concentrations) are substituted for methiothepin. Filter-bound radioactivity is determined by scintillation spectrometry on a beta counter. The data are analyzed using a non-linear, iterative curve-fitting computer program (Bowen *et al.* 1995) to determine the compound affinity parameter. The concentration of the compound needed to inhibit the [^{125}I]DOI binding by 50% of the maximum is termed the IC_{50} or K_i value. Compounds are considered to possess high affinity for the 5-HT_2 receptor if their IC_{50} or K_i values are ≤50 nM.

Example 4 5-HT_2 Functional Assay: Phosphoinositide (PI) turnover assay

The relative agonist activity of serotonergic compounds at the 5-HT_2 receptor can be determined in vitro using the ability of the compounds to stimulate the production of

[^{3}H]inositol phosphates in [^{3}H]myo-inositol-labeled A7r5 rat vascular smooth muscle cells by their ability to activate the enzyme phospholipase C. These cells are grown in culture plates, maintained in a humidified atmosphere of 5% CO_2 and 95% air and fed semi-weekly with Dulbecco's modified Eagle medium (DMEM) containing 4.5 g/l glucose and supplemented with 2mM glutamine, 10 µg/ml gentamicin, and 10% fetal bovine serum. For the purpose of conducting the phosphoinositide (PI) turnover experiments, the A7r5 cells are cultured in 24-well plates as previously described (Griffin *et al.* 1998). Confluent cells are exposed for 24-30 hrs to 1.5 µCi [^{3}H]-myo-inositol (18.3 Ci/mmol) in 0.5 ml of serum-free medium. Cells are then rinsed once with DMEM/F-12 containing 10 mM LiCl prior to incubation with the test agent (or solvent as the control) in 1.0 ml of the same medium for 1 hr at 37°C, after which the medium is aspirated and 1 ml of cold 0.1 M formic acid added to stop the reaction. The chromatographic separation of [^{3}H]-inositol phosphates ([^{3}H]-IPs) on an AG- 1-X8 column is performed as previously described (Griffin *et al.* 1998) with sequential washes with H_2O and 50 mM ammonium formate, followed by elution of the total [^{3}H]-IPs fraction with 1.2 M ammonium formate containing 0.1 M formic acid. The eluate (4 ml) is collected, mixed with 15 ml scintillation fluid, and the total [^{3}H]-IPs determined by scintillation counting on a beta-counter. Concentration-response data are analyzed by the sigmoidal fit function of the Origin Scientific Graphics software (Microcal Software, Northampton, MA) to determine agonist potency (EC_{50} value) and efficacy (E_{max}). Serotonin (5-HT) is used as a positive control (standard) agonist compound and the efficacy of test compounds is compared to that of 5-HT (set at 100%). The concentration of the compound needed to stimulate the production of [^{3}H]-IPs by 50% of the maximum response is termed the EC_{50} value.

Compounds are considered potent agonists if their EC_{50} values in this functional assay are ≤ 1 μM and are considered full agonists if their efficacy is > 80% of that of 5-HT.

The above procedures were used to generate the data shown in Table 1.

Table 1. 5-HT2 Receptor Binding and Functional Data.

Compound	IC_{50}, nM	EC_{50}, nM	Efficacy (E_{max}, %)
(R)-DOI	0.46	277	82
Example 1	4.0	967	30

Example 5 Acute IOP Response in Lasered (Hypertensive) Eyes of Conscious Cynomolgus Monkeys

Intraocular pressure (IOP) can be determined with an Alcon Pneumatonometer after light corneal anesthesia with 0.1% proparacaine. Eyes are washed with saline after each measurement. After a baseline IOP measurement, test compound is instilled in one 30 μL aliquot to the right eyes only of nine cynomolgus monkeys. Vehicle is instilled in the right eyes of six additional animals. Subsequent IOP measurements are taken at 1, 3, and 6 hours.

Example 6 5-HT_{1A} Receptor Binding Assay

5-HT_{1A} binding studies were performed with human cloned receptors expressed in Chinese hamster ovary (CHO) cells using (^{3}H)8-OH DPAT as the ligand. Membranes from Chinese hamster ovary cells (CHO) expressing cloned 5-HT_{1A} receptors (manufactured for NEN by Biosignal, Inc., Montreal, Canada) were homogenized in approximately 40 volumes of 50 mM Tris pH 7.4 for 5 sec. Drug dilutions were made using a Beckman Biomek 2000 robot (Beckman Instruments, Fullerton, CA). Incubations

were conducted with membrane prep, test compounds, and 0.25 nM [^{3}H]8-OH-DPAT (NEN, Boston, MA) in the same buffer at 27°C for 1 h. Assays were terminated by rapid vacuum filtration over Whatman GF/B glass fiber filters pre-soaked in 0.3% polyethyleneimine. Bound radioactivity was measured using liquid scintillation spectrometry. Data were analyzed using non-linear curve fitting programs (Sharif *et al.* 1999).

Ligand binding studies can also be run using membrane preparations from calf and rat brain (local source) and human cortex membranes. Specific brain regions were dissected out, homogenized in 10 volumes of 0.32 M sucrose and centrifuged for 10 min at 700 x g. The resulting supernatant was centrifuged at 43,500 x g for 10 min and the pellet re-suspended in 50 mM Tris-HCl (pH 7.7, 25°C) using a 10 sec polytron treatment. Aliquots were stored at –140° C. To remove endogenous serotonin, the preps were incubated at 37° C for 10 min prior to the experiment. Assay incubations were terminated by rapid filtration over Whatman GF/C filters using a Brandel cell harvester. K_i values were calculated using the Cheng-Prusoff equation (De Vry *et al.* 1998).

Example 7 5-HT$_{1A}$ Functional Assays

The function of Compounds of the present invention can be determined using a variety of methods to assess the functional activity of 5-HT$_{1A}$ agonists. One such assay is performed using hippocampal slices from male Sprague-Dawley rats, measuring the inhibition of forskolin-stimated adenylate cyclase (Lopez-Rodriguez *et al.* 1999; Morin *et al.* 1991; De Vry *et al.* 1998). Rat hippocampal membranes were homogenized in 25 volumes of 0.3 M sucrose containing 1mM EGTA, 5 mM EDTA, 5 mM dithiothreitol, and

20 mM Tris-HCl, pH 7.4 at 25°C. The homogenate was centrifuged for 10 m in at 1,000 x *g*. The supernatant subsequently was centrifuged at 39,000 x g for 10 min. The resulting pellet was re-suspended in homogenization buffer at a protein concentration of approximately 1 mg/ml and aliquots were stored at –140°C. Prior to use, the membranes were rehomogenized in a Potter-Elvehjem homogenizer. Fifty µl of the membrane suspension (50 µg protein) were added to an incubation buffer containing 100 mM NaCl, 2 mM magnesium acetate, 0.2 mM ATP, 1 mM cAMP, 0.01 mM GTP, 0.01 mM forskolin, 80 mM Tris-HCl, 5 mM creatine phosphate, 0.8 U/µl creatine phosphokinase, 0.1 mM IBMX, 1-2 µCi α-[^{32}P]ATP. Incubations with test compounds (10 min at 30°C) were initiated by the addition of the membrane solution to the incubation mixture (prewarmed 5 min at 30°C). [^{32}P]cAMP was measured according to the method of Salomon (Salomon 1979). Protein was measure using the Bradford assay (Bradford 1976).

Functional activity can also be determined in recombinant human receptors according to the method of Schoeffter *et al.* (1997). HeLa cells transfected with recombinant human 5-HT_{1A} receptors were grown to confluence in 24-well plates. The cells were rinsed with 1 ml of Hepes-buffered saline (in mM) NaCl 130, KCl 5.4, $CaCl_2$, 1.8, $MgSO_4$ 0.8, NaH_2PO_4 0.9, glucose 25, Hepes 20, pH 7.4, and phenol red 5 mg/l. The cells were labelled with 6 µCi/ml of [^{3}H] adenine (23 Ci/mmol, Amersham, Rahn AG, Zurich, Switzerland) in 0.5 ml of saline at 37 °C for 2 hr. The plates were subsequently rinsed twice with 1 ml of buffered saline containing 1mM isobutylmethylxanthine. The cells were incubated for 15 min in 1 ml of this solution (37 °C) in the presence or absence of 10 µM forskolin and the test compound. The buffer was then removed and 1 ml of 5% trichloroacetic acid (TCA) containing 0.1 mM cAMP and 0.1 mM ATP was added to

extract the samples. After 30 min at 4°C, the TCA extracts were subjected to chromatographic separation on Dowex AG 50W-X4 and alumina columns (Salomon 1991). Cyclic AMP production was calculated as the ratio [^{3}H]cAMP/([^{3}H]cAMP + [^{3}H]ATP).

Table 2. 5-HT1A Receptor Binding and Functional Data.

Compound	IC_{50}, nM	EC_{50}, nM	Efficacy (E_{max}, %)
(R)-8-OH-DPHAT	0.52	2.6	102
Example 1	6.4	110	94

Example 8 Alpha-2 Adrenergic Receptor Assay Methods

Cell culture. For the alpha-2A assays, HT29 human clonic adenocarcinoma cells were grown in McCoy's 5A Medium Modified supplemented with 10% (v/v) heat-inactivated fetal bovine serum in a humidified atmosphere of 5% CO_2/95% air. Cells were sub-cultured with 0.5% Trypsin/5.3 mM EDTA in 48 wells plates with confluence being reached in approximately 4 days. Growth medium was replaced with fresh medium, 24 hours before assay of confluent cells in order to avoid the nutrient exhaustion.

Cyclic AMP functional assays. Confluent cultures of HT29 cells were washed twice with 0.5 ml of 15mM Hepes-buffered DMEM (DMEM/F12), then incubated with 0.5 ml DMEM/F12 containing 0.25mM 3-Isobutyl-1-methyl-xanthine (IBMX) for 20 minutes. At the end of this period the appropriate serially diluted α2-adrenergic agonists was added and the cells were further incubated for 10 minutes. Then the appropriate concentration of forskolin (for HT29 cells 4μM) was added and the cells were incubated

for an additional 10 minutes. At the end of the incubation period the media was aspirated and 150 µl of 0.1 M acetic acid, pH 3.5 was added. The plates were incubated at 4o C for 20 minutes. Then 220 µl of 0.1 M sodium acetate, pH 11.5-12 was added. The plates were stored at –20° C. After this, a commercially available cAMP ELISA kit was used to quantify the amount of cAMP generated in the receptor assay. In all these alpha-2 receptor assays, an inhibition of cAMP production reflected a receptor-mediated process.

Table 3. Alpha2A Receptor Binding and Functional Data.

Compound	EC_{50}, nM	Efficacy (E_{max}, %)
Brimonidine	22	100
Example 1	110	62

All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and structurally related may be substituted for the agents described herein to achieve similar results. All such substitutions and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

References

The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

United States Patents

5,494,928

5,571,833

5,578,612

5,874,477

5,902,815

Foreign Patents and Published Applications

EP 0771563A2.

PCT/US99/19888

WO 92/0338

WO 97/35579

WO 98/18458

WO 98/31354 A2

WO 00/16761

WO 01/70223 A1

Other Publications

Bowen *et al.*, TRENDS PHARMACOL. SCI., 16:413 (1995).

Bradford, ANAL. BIOCHEM 72:248-254 (1976).

De Vry *et al.*, J. PHARM. EXPER. THER. 284(3):1082-1094 (1998).

Fiorella *et al.*, PSYCHOPHARM. 121(3):347-356 (1995).

Griffin *et al.*, J. PHARMACOL. EXPT. THER. 286(1):411-418 (1998).

Hoyer *et al.*, PHARMACOL. REV. 46:157-203 (1994).

Johnson *et al.*, NEUROPHARMACOLOGY, 26(12):1803-1806 (1987).

Lopez-Rodriguez *et al.*, J. MED. CHEM. 42(1):36-49 (1999).

Martin *et al.*, TRENDS PHARMACOL. SCI. 19:2-4 (1998).

Morin *et al.*, J. NEUROCHEM. 56(4):1114-1120 (1991).

Osborne, *et al.*, OPHTHALMOLOGICA, 210:308-314 (1996).

Salomon, ADV. CYCLIC NUCLEOTIDE RES. 10:35-55 (1979).

Salomon, METHODS IN ENZYMOLOGY 195: 22-28 (1991).

Schoeffter *et al.* NEUROPHARM. 36:429-437 (1997).

Sharif *et al.*, J. PHARMAC. PHARMACOL. 51: 685-694 (1999).

Tobin *et al.*, J. NEUROSCI. 8:3713-3721 (1988).

Wang *et al.*, ARCH. OPHTHALMOL. 111:535-538 (1993).

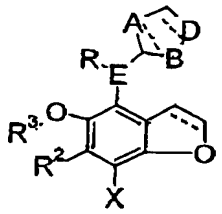
Wang, *et al.*, CURRENT EYE RESEARCH, 16(8):769-775 (1997).

Wang *et al.*, IVOS, 39(4), S488 (1998).

Zifa and Fillion, PHARMACOL. REV. 44:401-458 (1992).

We Claim:

1. A compound of the formula:



wherein A, B and D are independently chosen from either N or C, with the provision that at least one of A, B or D is N;

E is C or N;

R is H or C_{1-4}alkyl;

R^2 and R^3 are independently H, C_{1-3} alkyl, C_{2-3} alkenyl, or R^2 and R^3 taken together can form a 5 or 6 member ring;

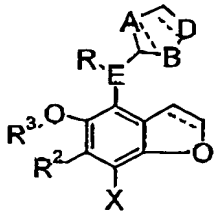
X is hydrogen, halogen, C_{1-4}alkyl, or CF_3; and

the dashed bond may be a single bond or a double bond;

and pharmaceutically acceptable salts and solvates.

2. The compound of claim 1, wherein the compound is 2-(8-bromo-benzo-[1,2-b;4,5-b']difuran-4-yl) imidazoline hydrochloride.

3. A method for lowering intraocular pressure and providing neuroprotection comprising administering to a patient in need thereof a therapeutically effective amount of a composition comprising a compound of the formula:



wherein A, B and D are independently chosen from either N or C, with the provision that at least one of A, B or D is N;

E is C or N;

R is H or C_{1-4}alkyl;

R^2 and R^3 are independently H, C_{1-3} alkyl, C_{2-3} alkenyl, or R^2 and R^3 taken together can form a 5 or 6 member ring;

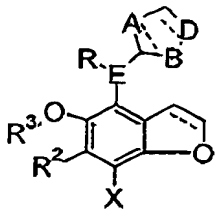
X is hydrogen, halogen, C_{1-4}alkyl, or CF_3; and

the dashed bond may be a single bond or a double bond;

and pharmaceutically acceptable salts and solvates.

4. The method of claim 3, wherein the compound is 2-(8-bromo-benzo-[1,2-b;4,5-b"]difuran-4-yl) imidazoline hydrochloride.

5. A composition for lowering and controlling normal or elevated intraocular pressure and providing ocular neuroprotection, comprising a compound of the formula:



wherein A, B and D are independently chosen from either N or C, with the provision that at least one of A, B or D is N;

E is C or N;

R is H or C_{1-4}alkyl;

R^2 and R^3 are independently H, C_{1-3} alkyl, C_{2-3} alkenyl, or R^2 and R^3 taken together can form a 5 or 6 member ring;

X is hydrogen, halogen, C_{1-4}alkyl, or CF_3; and

the dashed bond may be a single bond or a double bond;

and pharmaceutically acceptable salts and solvates.

6. The composition of claim 5, wherein the compound is 2-(8-bromo-benzo-[1,2-b;4,5-b"]difuran-4-yl) imidazoline hydrochloride.

7. The composition of claim 6, further comprising ophthalmologically acceptable preservatives.

8. The composition of claim 6, further comprising ophthalmologically acceptable surfactants.

9. The composition of claim 6, further comprising an agent to increase viscosity.

10. The composition of claim 9, wherein the agent is selected from the group consisting of hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, and polyvinylpyrrolidone.

11. The composition of claim 6, further comprising ophthalmologically acceptable preservatives, ophthalmologically acceptable surfactants and at least one agent to increase viscosity.

12. The composition of claim 6, further defined as a topical ophthalmic suspension or solution having a pH of about 5 to about 8.

13. The composition of claim 12, wherein the concentration of the compound is from .01% to 5% by weight.

14. The composition of claim 13, wherein the composition of the compound is from .25% to 2% by weight.

15. The composition of claim 6, further comprising at least one agent selected from the group consisting of β-blockers, prostaglandins, carbonic anhydrase inhibitors, and miotics.

16. The composition of claim 6, further comprising at least one agent selected from the group consisting of calcium channel blockers and NMDA antagonists.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/39316

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/4178; C07D 403/06
US CL : 514/397; 548/311.4
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/397; 548/311.4

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CA 2,036,975 A1 (LANG) 28 August 1991 (28/08/91), see entire document, especially page 1 and pages 23-24.	1-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
05 February 2003 (05.02.2003)	25 FEB 2003
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Laura L. Stockton, Ph.D. Telephone No. 703/308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

DECLARATION AND POWER OF ATTORNEY

As the below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original and first inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled:

NOVEL BENZODIFURANIMIDAZOLINE AND BENZOFURANIMIDAZOLINE DERIVATIVES AND THEIR USE FOR THE TREATMENT OF GLAUCOMA

described and claimed in the specification identified as Attorney Docket No. 2345F USA, which is a national application under 35 U.S.C. § 371 of PCT Application Serial No. PCT/US02/39316 filed December 9, 2002, which draws priority from U.S. Provisional Application Serial No. 60/343,378 filed December 20, 2001 (the "Prior Applications") now abandoned.

The specification of Attorney Docket No. 2345F USA (check one)

( ) is attached hereto.
(X) was filed by an authorized person on my behalf on December 9, 2002 as Application Serial No. PCT/US02/39316

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56(a).

Pursuant to C.F.R. Section 1.56(a) I acknowledge my duty to disclose information of which I am aware material to the patentability of the subject matter of this application. I do not know and do not believe that the same was ever known or used in the United States of America before my invention thereof or patented or described in any printed publication in any country before my invention thereof, or more than one year prior to said Prior Applications, or in public use or on sale in the United States of America more than one year prior to said Prior Applications. Upon information and belief, said subject matter has not been patented or made the subject of an inventor certificate issued before the date of said Prior

Applications in any country foreign to the United States of America or on an application filed by me or my legal representatives or assigns more than twelve months prior to said Prior Applications.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint **Barry L. Copeland, Reg. No. 34,801**; James A. Arno, Reg. No. 26,145; Gregg C. Brown, Reg. No. 30,613; Jeffrey S. Schira, Reg. No. 34,922; Patrick M. Ryan, Reg. No. 36,263; W. David Lee, Reg. No. 39,743, Teresa J. Schultz, Reg. No. 40,526, and Armando Pastrana, Jr., Reg. No. 44997 of Alcon, 6201 South Freeway, Fort Worth, TX 76134, my attorneys, with full power of substitution and revocation, to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith

Full name of joint inventor:	ZIXIA FENG
Address:	4204 Hideaway Drive Arlington, Texas 76017 United States of America
Inventor's Signature:	
Date:	6-11-04
Citizenship:	United States of America

Full name of joint inventor:	MARK R. HELLBERG
Address:	3002 Oak Cove Road Arlington, Texas 76017 United States of America
Inventor's Signature:	
Date:	6-10-04
Citizenship:	United States of America

ATTACHMENT B

IN THE UNITED STATES PATENT OFFICE

In re: FENG ET AL.

Serial No. NYA

Filed: June 14, 2004

For: NOVEL BENZODIFURANIMIDAZOLINE AND BENZOFURANIMIDAZOLINE DERIVATIES AND THEIR USE FOR THE TREATMENT OF GLAUCOMA

PETITION UNDER 37 CFR 1.10

MS PCT
ATTENTION: PCT LEGAL
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants hereby petition the Director to accord the enclosed correspondence, which consists of filing papers for a §371 patent application, a filing date of June 14, 2004.

1. Applicants' §371 patent application was mailed to the USPTO using the USPS "Express Mail Post Office to Addressee" service with sufficient postage on June 14, 2004. The USPS Express Mail item number is EV224562394US.

2. Since a filing receipt had not been received and Applicants' postcard not returned, telephone calls were made by a legal assistant in Alcon's R&D Counsel and IP Law Department to the USPCT Help Desk on or about November 9, 2004, and subsequently on or about December 7, 2004, to inquire about the status of Applicants' §371 patent application. Both telephone calls confirmed that the USPTO was not able to locate any information about Applicants' §371 patent application.

3. Nevertheless, Applicants' application papers were successfully received at the Patent Office on June 15, 2004, as evidenced by the USPS records. A true copy

of the USPS delivery information for Express Mail item number EV224562394US is attached as Ex. A; this information shows that a USPTO representative "Mary Boston" signed for Express Mail item EV224562394US on June 15, 2004 at 10:25 AM in Alexandria, Virginia.

4. Upon the advice of the PCT Help Desk, Applicants' hereby file this Petition pursuant to 37 CFR 1.10, addressed to the PCT Legal Office, and resubmit Applicants' §371 application.

5. This Petition is filed after concluding in December 2004 that Applicants' §371 patent application, which was forwarded to the USPTO on June 14, 2004 (Applicants' Docket No. 2345 US), via USPS Express Mail Air bill EV 224562394 US, was misplaced or cannot be located at the PTO.

6. Attached as Ex. B is a true copy of the USPS Express Mail mailing label EV 224562394 US. This label shows a "date-in" of Applicants' §371 patent application of June 14, 2004, and a "day of delivery" of June 15, 2004. In the upper right hand corner, this label clearly bears the circular date stamp of the USPS' Burleson, TX office with a received date of June 14, 2004.

7. Attached as Ex. C is a true copy of Alcon's Express Mail Corporate Account Mailing Statement showing that Express Mail item number EV224562394US was mailed on June 14, 2004, from Zip Code 76028 to Zip Code 22313. This Statement also shows that the postage charged to Alcon's account on June 14, 2004, for Express Mail item number EV224562394US was $13.65.

8. Attached as Ex. D is a true copy of Alcon's internal log of Express Mail items showing that Express Mail item number EV224562394US was deposited with the USPS in Burleson, TX on June 14, 2004, at 4:56 PM. This log bears the initials "ss" which are the initials of one of the legal assistants in Alcon's R&D Counsel and IP Law Department.

Express Mail No. EV 484447825US

9. Attached as Ex. E are true copies of the papers originally filed with USPTO on June 14, 2004, in Express Mail item number EV224562394US:

A. Transmittal Letter to the United States Designated/Elected Office (DO/EO/US) Concerning a Filing under 35 U.S.C. 371 (Form PTO-1390), two pages, in duplicate;

B. Declaration and Power of Attorney (2 pages); and

C. Return post card (not returned to Applicants) showing Express Mail No. EV224562394 US. This return post card identifies the contents of Express Mail item number EV224562394 US as: Transmittal Letter to the US Designated/Elected Office Concerning a Filing Under 35 USC 371 (2 pages, in duplicate), Declaration and Power of Attorney (2 pages), Return Post Card.

Should the Director require any additional information concerning this Petition, please contact the undersigned.

Respectfully submitted,

ALCON RESEARCH, LTD.

Date: 1/26/05 By: _____
Patrick M. Ryan
Reg. No. 36,263

Address for Correspondence:
Patrick M. Ryan
Assistant General Counsel
IP Legal Department
Alcon Research, Ltd.
6201 South Freeway
Fort Worth, TX 76134-2099
T: 817-551-3066
F: 817/551-4610

EXHIBIT A

UNITED STATES POSTAL SERVICE

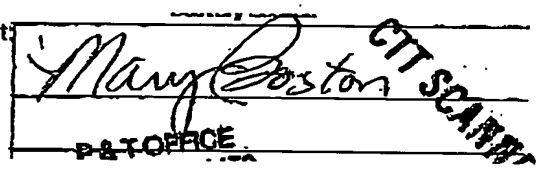
Date: 11/12/2004

Fax Transmission To: Postal Customer
Fax Number: 817-551-4610

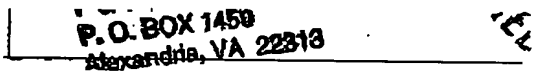
Dear Postal Customer:

The following is in response to your 11/12/2004 request for delivery information on your Express Mail item number EV224562394US. The delivery record shows that this item was delivered on 06/15/2004 at 10:25 AM in ALEXANDRIA, VA 22313 to M BOSTON. The scanned image of the recipient information is provided below.

Signature of Recipient:



Address of Recipient:



Thank you for selecting the Postal Service for your mailing needs. If you require additional assistance, please contact your local Post Office or postal representative.

Sincerely,

United States Postal Service

EXHIBIT B

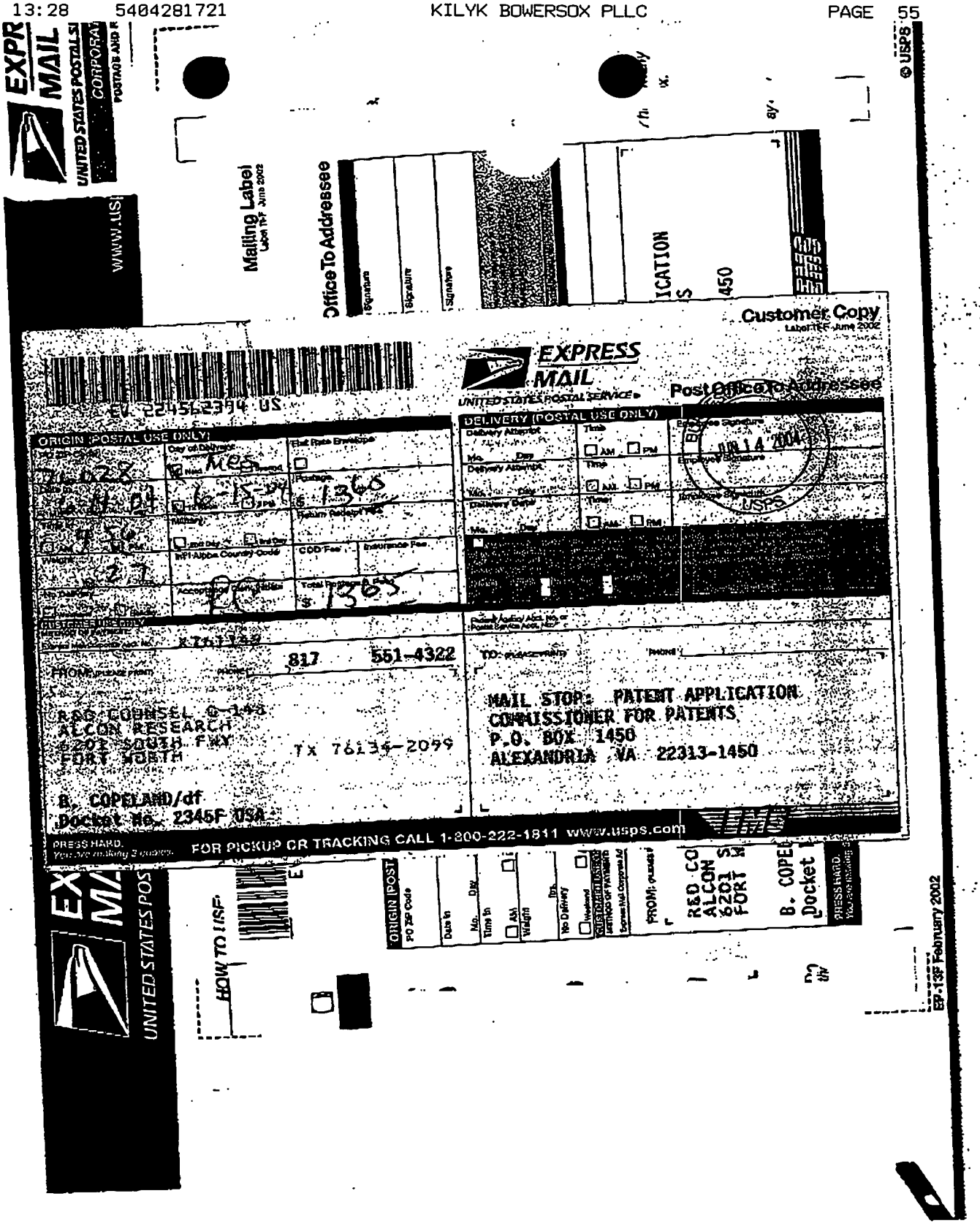

EXPRESS MAIL
UNITED STATES POSTAL SERVICE
Mailing Label
Office To Addressee
Customer Copy
EV 224562394 US
ORIGIN (POSTAL USE ONLY)
DELIVERY (POSTAL USE ONLY)
Post Office To Addressee
JUN 14 2004
USPS
817 551-4322
R&D COUNSEL Q-148
ALCON RESEARCH
6201 SOUTH FWY
FORT WORTH TX 76134-2099
MAIL STOP: PATENT APPLICATION
COMMISSIONER FOR PATENTS
P.O. BOX 1450
ALEXANDRIA VA 22313-1450
B. COPELAND/df
Docket No. 2345F USA
PRESS HARD.
FOR PICKUP OR TRACKING CALL 1-800-222-1811 www.usps.com
HOW TO USE
EP-13F February 2002

EXHIBIT C

EXPRESS MAIL

"D STATES POSTAL SERVICE ®

PAGE: 1

EXPRESS MAIL CORPORATE ACCOUNT
MAILING STATEMENT

ACCOUNT NO: 761149 PERIOD: 06/01/04 - 06/30/04

DATE	CHARGE BACK	LABEL NUMBER	ORIG ZIP	DEST ZIP	APPLIED REFUND	POSTAGE	FEES PAID	FEES WAIVED	DEPOSITS	MISC WITHDRAWALS	CODA REC
BEGINNING BALANCE:						609.70					
05/28/04		EV224560610US	76134	22313		13.65					
05/28/04		EV224560623US	76134	22313		13.65					
05/28/04		EV224560637US	76134	22313		13.65					
05/28/04		EV224560645US	76134	22313		13.65					
05/28/04		EV224560654US	76134	22313		13.65					
05/28/04		EV224560668US	76134	22313		13.65					
06/02/04		EV224561915US	76134	22313		17.85					
06/08/04		EV224561924US	76134	22313		13.65					
06/08/04		EV224562099US	76134	22313		13.65					
06/08/04		EV224562108US	76134	22313		13.65					
06/08/04		EV225497207US	76134	22313		17.85					
06/14/04		EV011108272US	76028	22313		13.65					
06/14/04		EV011108286US	76028	22313		13.65					
06/14/04		EV224560708US	76028	22313		21.05					
06/14/04		EV224562125US	76028	22313		13.65					
06/14/04		EV224562139US	76028	22313		13.65					
06/14/04		EV224562394US	76028	22313		13.65					
06/14/04		EV224562417US	76028	22313		13.65					
06/14/04		EV224562425US	76028	22313		21.05					
06/14/04		EV224562434US	76028	22313		13.65					
06/16/04		EV224562111US	76028	22313		13.65					
06/16/04		EV224562156US	76028	22313		13.65					
06/17/04		EV224562585US	76028	22313		13.65					
06/17/04		EV225496759US	76028	22313		13.65					
06/18/04		EV224562148US	76134	22313		13.65					
06/18/04		EV224562160US	76134	22313		13.65					
06/23/04		EV011108414US	76134	22313		17.85					
06/24/04		EV224561972US	76134	22313		13.65					
06/25/04		EV011108241US	76134	22313		13.65					
06/25/04		EV224562241US	76134	22313		13.65					
06/28/04		EV224561969US	76134	22313		21.05					
06/28/04		EV224561986US	76134	22313		13.65					
06/29/04		EV224562275US	76134	22313		13.65					
06/30/04		EV011108374US	76134	22313		13.65					
06/30/04		EV224562289US	76134	22313		13.65					
SUB-TOTAL:						512.55					
(A) TOTAL CHARGES:						512.55	0.00	0.00			
(B) TOTAL ADJUSTMENTS (±):						0.00	0.00	0.00			
(C) TOTAL REFUNDS (±):						0.00	0.00	0.00			
TOTAL (A + B - C):						512.55	0.00	0.00			
ENDING BALANCE:						97.15					

EXHIBIT D

EXPRESS MAIL DELIVERIES TO PTO

Express Mail #	Docket #	Deposit Made: Place	Date	Time	Time of Last P/U for Day	Depositor's Initials	Entry In Log Made: Date	Time
EV224560608US	2438FWO	Seminary	5-28-04	4:43		DWS	6-1-04	8:39am
EV224560604US	2558FWO	"	"	"		"	"	"
EV224560664US	2437FWO	"	"	"		"	"	"
EV224560637US	2436FWO	"	"	"		"	"	"
EV224560623US	2428FWO	"	"	"		"	"	"
EV224561915US	1848 US	Seminary	6-2-04	4:30pm		TA	6-4-04	11:06AM
EV224562099US	2165 US	Seminary	6-8-04	12:15p		DF	6-8-04	1:03p
EV224597209US	2165FWO	Seminary	6-8-04	12:14p		DF	6-8-04	1:04p
EV224561924US	2507FWO	Seminary	6-8-04	12:13p		DF	6-8-04	1:05p
EV224562108US	2587 US	Seminary	6-8-04	12:12p		DF	6-8-04	1:05p
EV224562139US	2475 US	Suresan	6-14-04	5:01		DW	6-15-04	8:45p
EV224562125US	2475 PCT	✓	✓	5:00		DW	✓	✓
EV224560708US	2338 US F	✓	✓	4:59		DW	✓	✓
EV224562425US	2306 F US	✓	✓	4:58		DW	✓	✓
EV224562394US	2345 F US	✓	✓	4:56		DW	✓	✓
EV224562434US	2306 F US	✓	✓	4:55		DW	✓	✓
EV224562417US	2336 F US	✓	✓	4:53		DW	✓	✓
EV011108272US	2705	✓	✓	4:52		DW	✓	✓

EXHIBIT E

FORM PTO-1390 (REV. 10-2003) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (If known, see 37 CFR 1.5
2345F USA	NYA

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US02/39316	09 December 2002 (09.12.02)	20 December 2001 (20.12.01)

TITLE OF INVENTION: NOVEL BENZODIFURANIMIDAZOLINE AND BENZOFURANIMIDAZOLINE DERIVATIVES AND THEIR USE FOR THE TREATMENT OF GLAUCOMA

APPLICANT(S) FOR DO/EO/US: Zixia FENG and Mark R. HELLBERG

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☑ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☑ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☐ The US has been elected (Article 31).
5. ☑ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☐ has been communicated by the International Bureau.
   c. ☑ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☑ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A preliminary amendment.
14. ☐ An Application Data Sheet under 37 CFR 1.76.
15. ☐ A substitute specification.
16. ☐ A power of attorney and/or change of address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13*ter*.2 and 37 CFR 1.821 - 1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☐ Other items or information:

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
	PCT/US02/39316	2345F USA

21. ☐ The following fees are submitted:	CALCULATIONS PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):	
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO $1080.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO $920.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO $770.00	
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) $730.00	
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) $100.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 920.00
Surcharge of $130.00 for furnishing the oath or declaration later than 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	16 - 20 =	0	x $18.00	$ 0
Independent claims	3 - 3 =	0	x $86.00	$ 0
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $290.00	$
TOTAL OF ABOVE CALCULATIONS =				$ 920.00
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				$
SUBTOTAL =				$
Processing fee of $130.00 for furnishing the English translation later than 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$
TOTAL NATIONAL FEE =				$
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +				$
TOTAL FEES ENCLOSED =				$ 920.00
			Amount to be refunded:	$
			charged:	$

a. ☐ A check in the amount of $ _____ to cover the above fees is enclosed.

b. ☑ Please charge my Deposit Account No. 501051 in the amount of $ ~~938.00~~ 920 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☑ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 501051 . A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Alcon Research, Ltd.
Attn: Barry L. Copeland (O-148)
6201 South Freeway
Fort Worth, Texas 76134-2099
Telephone: 817/551-4322
Telefax: 817-551-4610

SIGNATURE

Barry L. Copeland
NAME

34,801
REGISTRATION NUMBER

FORM PTO-1390 (REV. 10-2003) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	
2345F USA	N/A	
INTERNATIONAL APPLICATION NO.	**INTERNATIONAL FILING DATE**	**PRIORITY DATE CLAIMED**
PCT/US02/39316	09 December 2002 (09.12.02)	20 December 2001 (20.12.01)

TITLE OF INVENTION NOVEL BENZODIFURANIMIDAZOLINE AND BENZOFURANIMIDAZOLINE DERIVATIVES AND THEIR USE FOR THE TREATMENT OF GLAUCOMA

APPLICANT(S) FOR DO/EO/US Zeda FENG and Mark R. HELLBERG

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☑ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☑ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☐ The US has been elected (Article 31).
5. ☑ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☐ has been communicated by the International Bureau.
   c. ☑ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☑ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A preliminary amendment.
14. ☐ An Application Data Sheet under 37 CFR 1.76.
15. ☐ A substitute specification.
16. ☐ A power of attorney and/or change of address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13*ter*.2 and 37 CFR 1.821 - 1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☐ Other items or information:

U.S. APPLICATION NO. (see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO. PCT/US02/39316	ATTORNEY'S DOCKET NUMBER 2345F USA

21. ☐ The [illegible]ing fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):		CALCULATIONS PTO USE ONLY
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	$1080.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	$920.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$770.00	
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	$730.00	
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	$100.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =		$ 920.00
Surcharge of $130.00 for furnishing the oath or declaration later than 30 months from the earliest claimed priority date (37 CFR 1.492(e)).		$

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	16 - 20 =	1	x $18.00	$ 0
Independent claims	3 - 3 =	0	x $86.00	$ 0
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $290.00	$

TOTAL OF ABOVE CALCULATIONS =	$ 920.00
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.	$
SUBTOTAL =	$
Processing fee of $130.00 for furnishing the English translation later than 30 months from the earliest claimed priority date (37 CFR 1.492(f)).	$
TOTAL NATIONAL FEE =	$
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +	$
TOTAL FEES ENCLOSED =	$ 920.00
Amount to be refunded:	$
charged:	$

a. ☐ A check in the amount of $ _____ to cover the above fees is enclosed.

b. ☑ Please charge my Deposit Account No. 501051 in the amount of $ ~~838.00~~ 920 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☑ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 501051. A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Alcon Research, Ltd.
Attn: Barry L. Copeland (Q-148)
6201 South Freeway
Fort Worth, Texas 76134-2099
Telephone: 817/551-4322
Telefax: 817-551-4610

SIGNATURE

Barry L. Copeland
NAME

34,801
REGISTRATION NUMBER

DECLARATION AND POWER OF ATTORNEY

As the below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original and first inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled:

NOVEL BENZODIFURANIMIDAZOLINE AND BENZOFURANIMIDAZOLINE DERIVATIVES AND THEIR USE FOR THE TREATMENT OF GLAUCOMA

described and claimed in the specification identified as Attorney Docket No. 2345F USA, which is a national application under 35 U.S.C. § 371 of PCT Application Serial No. PCT/US02/39316 filed December 9, 2002, which draws priority from U.S. Provisional Application Serial No. 60/343,378 filed December 20, 2001 (the "Prior Applications") now abandoned.

The specification of Attorney Docket No. 2345F USA (check one)

( ) is attached hereto.

(X) was filed by an authorized person on my behalf on December 9, 2002 as Application Serial No. PCT/US02/39316

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims as amended by any amendment referred to above.

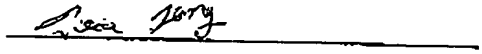
I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56(a).

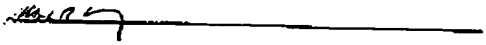
Pursuant to C.F.R. Section 1.56(a) I acknowledge my duty to disclose information of which I am aware material to the patentability of the subject matter of this application. I do not know and do not believe that the same was ever known or used in the United States of America before my invention thereof or patented or described in any printed publication in any country before my invention thereof, or more than one year prior to said Prior Applications, or in public use or on sale in the United States of America more than one year prior to said Prior Applications. Upon information and belief, said subject matter has not been patented or made the subject of an inventor certificate issued before the date of said Prior

Applications in any country foreign to the United States of America or on an application filed by me or my legal representatives or assigns more than twelve months prior to said Prior Applications.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint **Barry L. Copeland, Reg. No. 34,801**; James A. Arno, Reg. No. 26,145; Gregg C. Brown, Reg. No. 30,613; Jeffrey S. Schira, Reg. No. 34,922; Patrick M. Ryan, Reg. No. 36,263; W. David Lee, Reg. No. 39,743, Teresa J. Schultz, Reg. No. 40,526, and Armando Pastrana, Jr., Reg. No. 44997 of Alcon, 6201 South Freeway, Fort Worth, TX 76134, my attorneys, with full power of substitution and revocation, to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith

Full name of joint inventor:	ZIXIA FENG
Address:	4204 Hideaway Drive Arlington, Texas 76017 United States of America
Inventor's Signature:	
Date:	6-11-04
Citizenship:	United States of America

Full name of joint inventor:	MARK R. HELLBERG
Address:	3002 Oak Cove Road Arlington, Texas 76017 United States of America
Inventor's Signature:	
Date:	6-10-04
Citizenship:	United States of America

THE OFFICIAL DATE STAMP HEREON BY THE USPTO ACKNOWLEDGES RECEIPT OF THE FOLLOWING:

Title NOVEL BENZODIFURANIMIDAZOLINE AND BENZOFURANIMIDAZOLINE DERIVATIVES AND THEIR USE FOR THE TREATMENT OF GLAUCOMA

Applicant: FENG et al **Express Mail No:** EV224562394 US

Application No.: NYA **Confirmation No.:** NYA

Date of Filing Paper: JUNE 14, 2004

Enclosure(s): TRANSMITTAL LETTER TO THE US DESIGNATED/ELECTED OFFICE CONCERNING A FILING UNDER 35 USC 371 (2 PAGES, IN DUPLICATE), DECLARATION AND POWER OF ATTORNEY (2 PAGES), RETURN POST CARD

Docket No.: 2345F US **Initials:** BLC:df

26356
26356
PATENT TRADEMARK OFFICE

FORM PTO-1390 (REV. 10-2003) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
2345F USA	
U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	
NYA	
INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE
PCT/US02/39316	09 December 2002 (09.12.02)
PRIORITY DATE CLAIMED	
10 December 2001 (10.12.01)	

TITLE OF INVENTION: NOVEL BENZODIFURANIMIDAZOLINE AND BENZOFURANIMIDAZOLINE DERIVATIVES AND THEIR USE FOR THE TREATMENT OF GLAUCOMA

APPLICANT(S) FOR DO/EO/US: Zixia FENG and Mark R. HELLBERG

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☑ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☑ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☐ The US has been elected (Article 31).
5. ☑ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☐ has been communicated by the International Bureau.
   c. ☑ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☑ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A preliminary amendment.
14. ☐ An Application Data Sheet under 37 CFR 1.76.
15. ☐ A substitute specification.
16. ☐ A power of attorney and/or change of address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13*ter*.2 and 37 CFR 1.821 - 1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☐ Other items or information:

6/15/04 AF #9 MLR 6/04

U.S. APPLICATION [redacted] (37 CFR 1.5)	INTERNATIONAL APPLICATION NO. PCT/US02/39316 [redacted]	ATTORNEY'S DOCKET NUMBER 2345F USA

21. ☐ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):	CALCULATIONS PTO USE ONLY
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO $1080.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO $920.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO $770.00	
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) $730.00	
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) $100.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 920.00
Surcharge of $130.00 for furnishing the oath or declaration later than 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	16 - 20 =	1	x $18.00	$ 0
Independent claims	3 - 3 =	0	x $86.00	$ 0
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $290.00	$

TOTAL OF ABOVE CALCULATIONS =	$ 920.00
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.	$
SUBTOTAL =	$
Processing fee of $130.00 for furnishing the English translation later than 30 months from the earliest claimed priority date (37 CFR 1.492(f)).	$
TOTAL NATIONAL FEE =	$
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +	$
TOTAL FEES ENCLOSED =	$ 920.00
Amount to be refunded:	$
charged:	$

a. ☐ A check in the amount of $ _____ to cover the above fees is enclosed.

b. ☑ Please charge my Deposit Account No. 501051 in the amount of $ ~~938.00~~ 920 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☑ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 501051. A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Alcon Research, Ltd.
Attn: Barry L. Copeland (C-148)
6201 South Freeway
Fort Worth, Texas 76134-2099
Telephone: 817/551-4322
Telefax: 817-551-4610

SIGNATURE

Barry L. Copeland
NAME

34,801
REGISTRATION NUMBER

07 MAR 2005

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450
www.uspto.gov

Alcon Research
Attn: Barry L Copeland
6201 South Freeway
Fort Worth TX 76134-2099

In re Application of
FENG, Zixia et al.
Application No.: 10/525,410
PCT No.: PCT/US02/39316
Int. Filing Date: 09 December 2002
Priority Date: 20 December 2001
Docket No: 2345F USA
For: NOVEL ... TREATMENT OF GLAUCOMA

DECISION

ON PETITION UNDER

37 CFR 1.10(e)

This decision is in response to applicant's "Petition Under 37 CFR 1.10," filed in the United States Patent and Trademark Office on 26 January 2005. No petition fee is required.

BACKGROUND

On 09 December 2002, applicant filed international application PCT/US02/39316, claiming a priority date of 20 December 2001. The deadline for entry into the national stage in the United States was 21 June 2004 (20 June 2004 was a Sunday).

On 26 January 2005, applicant filed a petition under 37 CFR 1.10, accompanied by a transmittal letter, a copy of an express mail label and a declaration.

DISCUSSION

37 CFR 1.10(e) states:

> (e) Any person mailing correspondence addressed as set out in §1.1(a) to the Office with sufficient postage utilizing the "Express Mail Post Office to Addressee" service of the USPS but not received by the Office, may petition the Commissioner to consider such correspondence filed in the Office on the USPS deposit date, provided that:
>
> (1) The petition is filed promptly after the person becomes aware that the Office has no evidence of receipt of the correspondence;
>
> (2) The number of the "Express Mail" mailing label was placed on the paper(s) or fee(s) that constitute the correspondence prior to the original mailing by "Express Mail";
>
> (3) The petition includes a copy of the originally deposited paper(s) or fee(s) that constitute the correspondence showing the number of the "Express Mail" mailing label thereon, a copy of any returned postcard receipt, a copy of the "Express Mail" mailing label showing the "date-in," a copy of any other official notation by the USPS relied upon to show the date of deposit, and, if

the requested filing date is a date other than the "date-in" on the "Express Mail" mailing label or other official notation entered by the USPS, a showing pursuant to paragraph (d)(3) of this section that the requested filing date was the date the correspondence was deposited in the "Express Mail Post Office to Addressee" service prior to the last scheduled pickup for that day; and

(4) The petition includes a statement which establishes, to the satisfaction of the Commissioner, the original deposit of the correspondence and that the copies of the correspondence, the copy of the "Express Mail" mailing label, the copy of any returned postcard receipt, and any official notation entered by the USPS are true copies of the originally mailed correspondence, original "Express Mail" mailing label, returned postcard receipt, and official notation entered by the USPS.

Items (1) and (4) have been satisfied. The petition was filed promptly. Applicant states that the papers are a true copy of the earlier submission.

As to item (2), a review of the correspondence does not reveal the Express Mail mailing label number. See MPEP 513, III. "Express Mail" Mailing Label Number. Applicant indicates that the Express Mail mailing label number was on the postcard, but the postcard does not constitute correspondence filed with the Office.

As to item (3), applicant has provided what applicant claims to have submitted, along with an Express Mail log and corporate mail account records, but the original correspondence is not marked with the Express Mail mailing label number, and is not tied to the label that applicant has provided.

CONCLUSION

For the reasons set forth above, the petition under 37 CFR 1.10(e) is **DISMISSED** without prejudice.

Any reconsideration on the merits of this petition must be filed within **TWO (2) MONTHS** from the mail date of this decision. Any reconsideration request should include a cover letter entitled "Renewed Petition Under 37 CFR 1.10(e)."

The application is **ABANDONED**.

Any further correspondence with respect to this matter should be addressed to the Mail Stop PCT, Commissioner for Patents, Office of PCT Legal Administration, P.O. Box 1450, Alexandria, Virginia 22313-1450, with the contents of the letter marked to the attention of the Office of PCT Legal Administration.

Erin M. Pender

Erin M. Pender
Attorney Advisor
PCT Legal Administration

Telephone: 571-272-3292
Facsimile: 571-273-0459